LA-UR-14-22603
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Title:	Talk: Why Vaccines?
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Intended for:	Bette Korber's talk for UC Regents at LANL
Issued:	2014-04-17

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New Mexico Consortium

I. Why vaccines?

II. HIV's diversity and the implications for the challenge of vaccine design

III. Mosaic vaccine efficacy in macaques

IV. Looking Ahead

A vaccine triumph for mankind

We have eradicated smallpox, a disease that caused between 300-500 million deaths in the last century

Smallpox was ancient disease, and had been with us for at least 12,000 years

Those who survived were often scarred, and blinded

The very last case of smallpox was diagnosed Oct 26, 1977

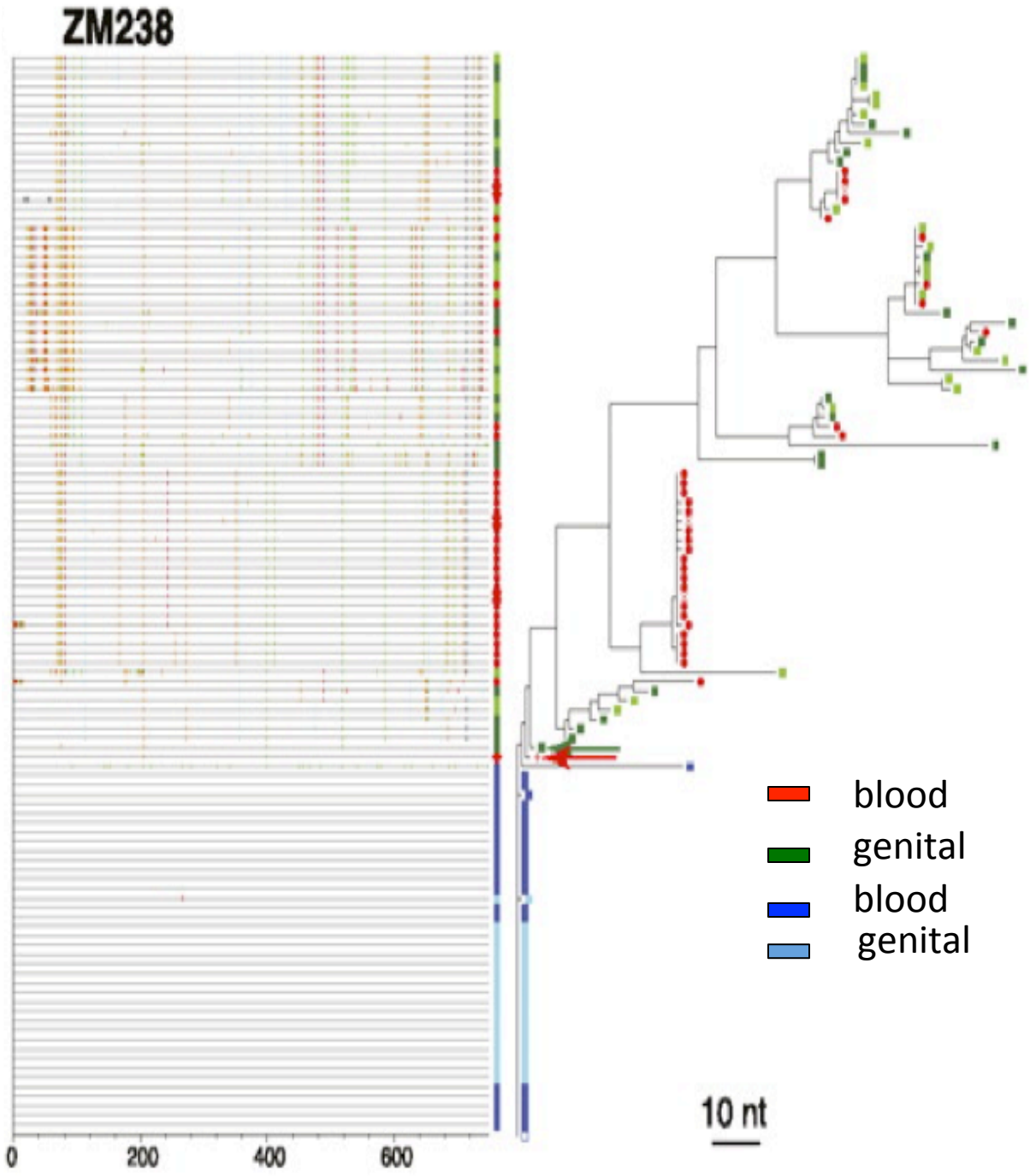
Vaccine Preventable Diseases licensed before 1980 in the USA

Disease	Peak annual cases	Peak annual deaths	2006 cases	2004 deaths
Diptheria	30,508	3,065	0	0
Measles	763,094	552	55	0
Mumps	212,932	50	6584	0
Pertussis	265,269	7,518	15,632	27
Polio, paralytic	21,269	3,145	0	0
Smallpox	110,672	2,510	0	0
Rubella	488,796	24	11	0
Tetanus	601	511	41	4

Rousch & Murphy JAMA 298:2155 (2007)

HIV phylogeny example

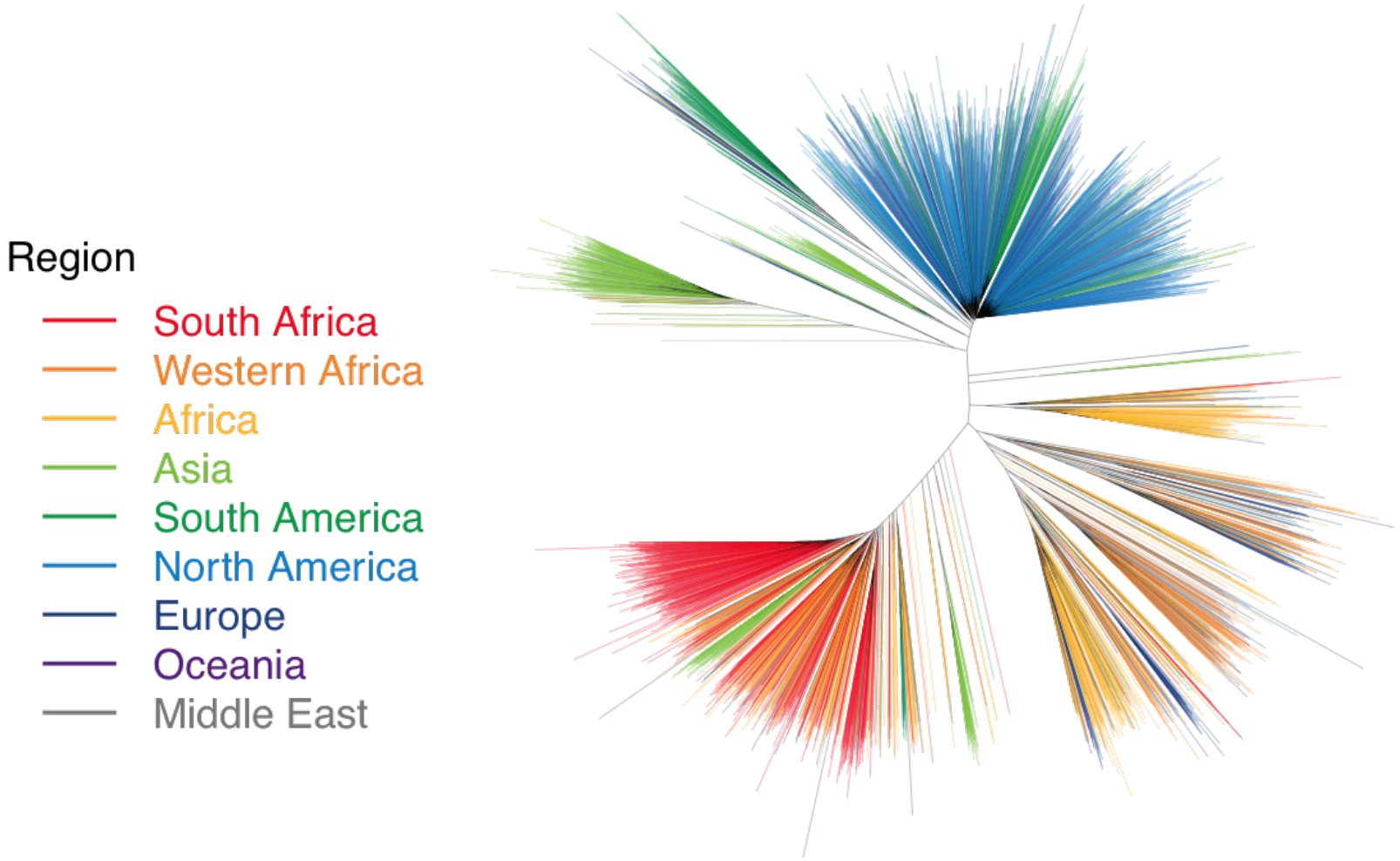
Donor/recipient transmission pair



Boeras et al. PNAS 2011 108 (46):E1156-63.
Role of donor genital tract HIV-1 diversity in the transmission bottleneck.

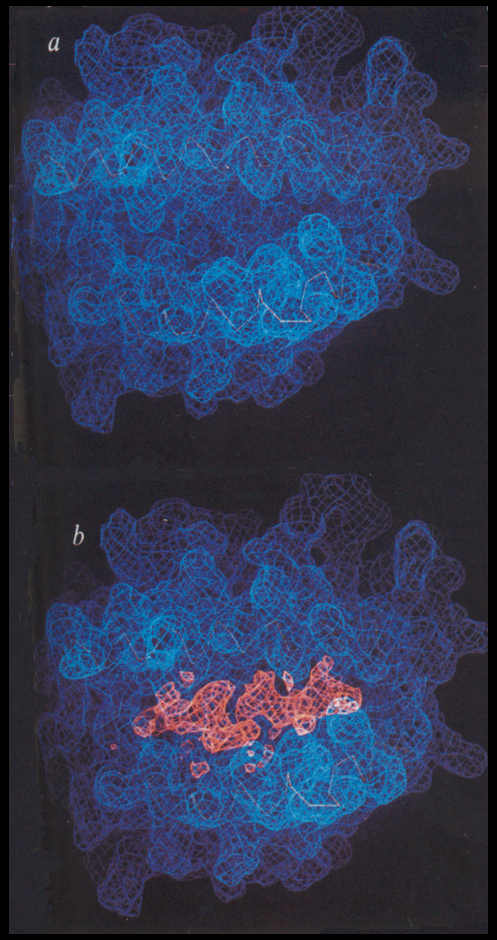
Peter Hraber, T6, LANL

LANL database: www.hiv.lanl.gov



Env phylogenies Peter Hraber
from annotated sequences from ~50,000 subjects

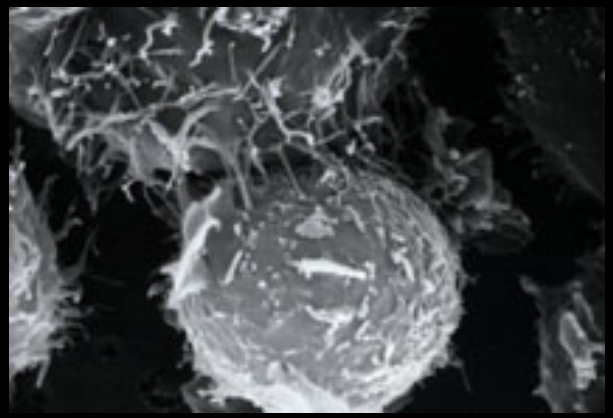
Cytotoxic T cells recognize contiguous fragment

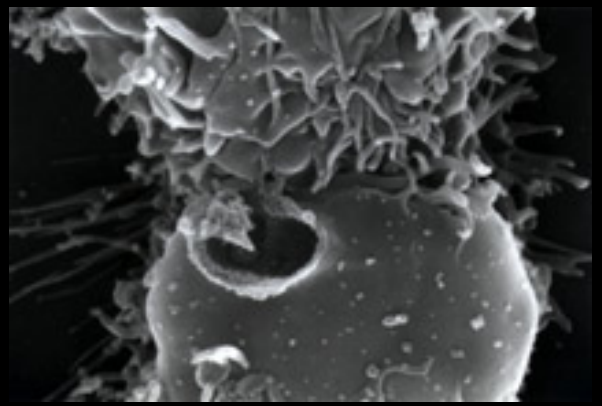


Killer T cells identify HIV infected cells

By recognizing small but contiguous fragments of viral protein carried to the cell surface by human class I proteins…

…they trigger infected cells to self destruct.

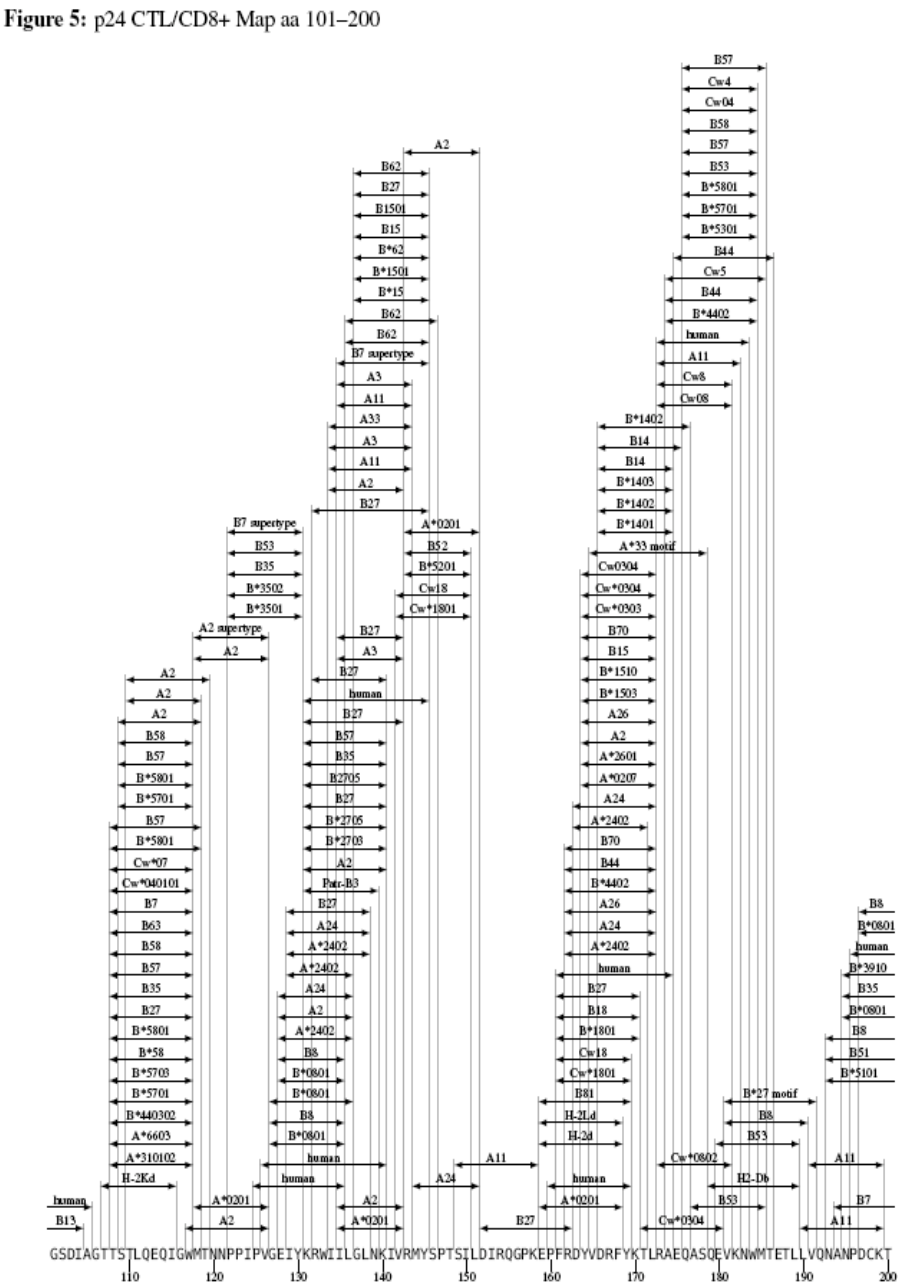




p24 positions100-200

LANL database map: known *CD8+ T-cell* responses densely populate HIV proteins

Thus *potential* T cell epitopes, PTEs, are defined as all 9-mers in an alignment



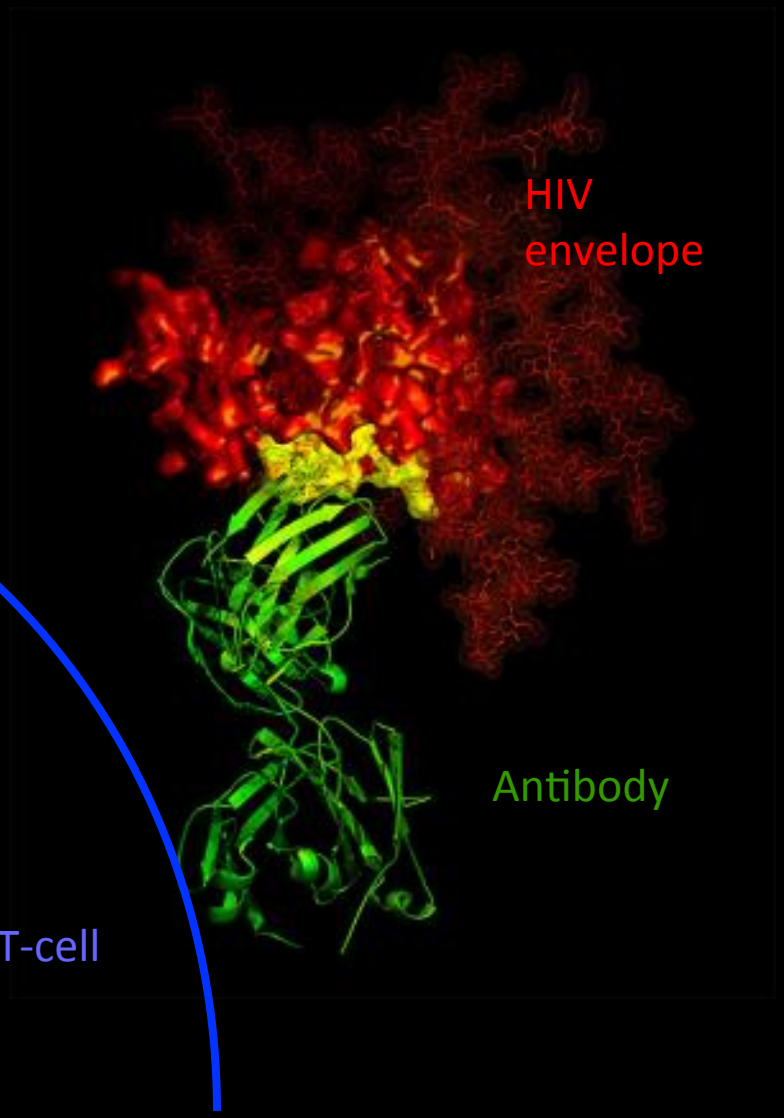
Cross-reactive neutralizing antibody responses can block infection target cells

Antibodies can bind directly to its envelope and keep it from entering our cells.

What is different from T cells:

- Discontinuous epitopes
- Somatic mutaton

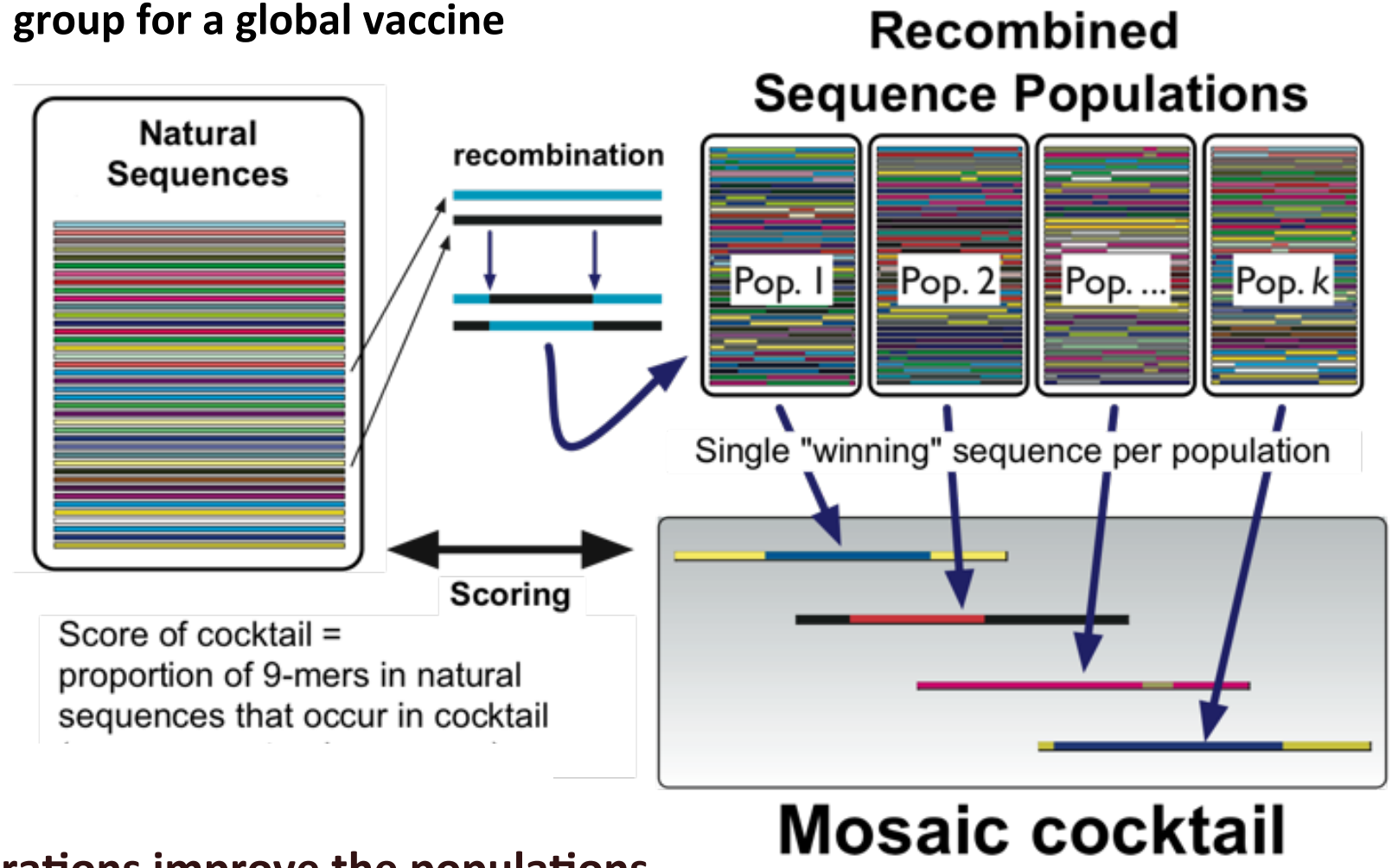
Mosaic Vaccines were optimized For T cells, but they can also elicit antibodies



Mimicking HIV Evolution by *in silico* Recombination: Using a Genetic Algorithm to Optimize Global Epitope Coverage

Fischer *et al*, *Nat Med* 13:100 (2007)

M group for a global vaccine



Iterations improve the populations, improve the cocktail

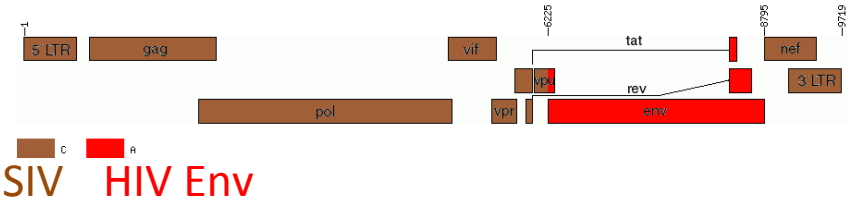
Simon Perkins, Will Fischer, James Theiler

Protective efficacy of a global HIV-1 mosaic vaccine against heterologous SHIV challenges in rhesus monkeys

Barouch et al., Cell 155(3):531-9. Oct. 2013

Challenge: Monkey Model

- SHIV: HIV Envelope in an SIV background so it infects macaques
- Only Env is shared
- Heterologous, virulent, hard to neutralize challenge: SHIV-SF162P3



Expose to SHIV

HIV Env, Gag, Pol

Vaccinate

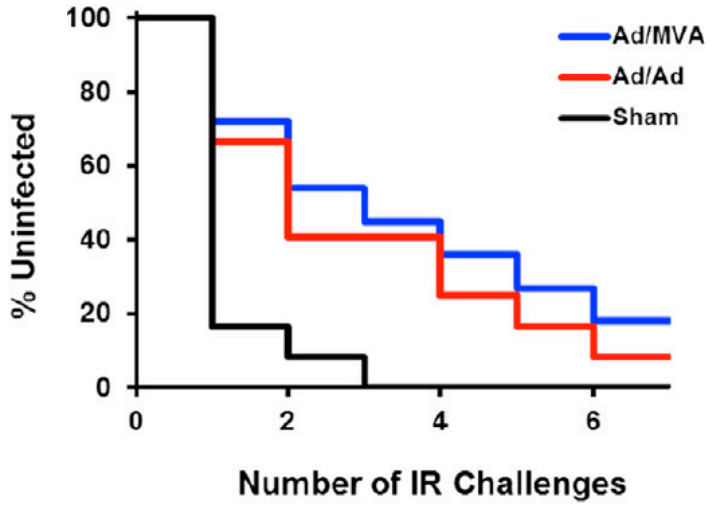
Vector:
Ad or MVA

Assess protection,
and correlates of protection

The mosaic vaccine inhibits infection

The rate
Of infection by
SHIV-SF162P3 is
>100 times that of
HIV through human sex

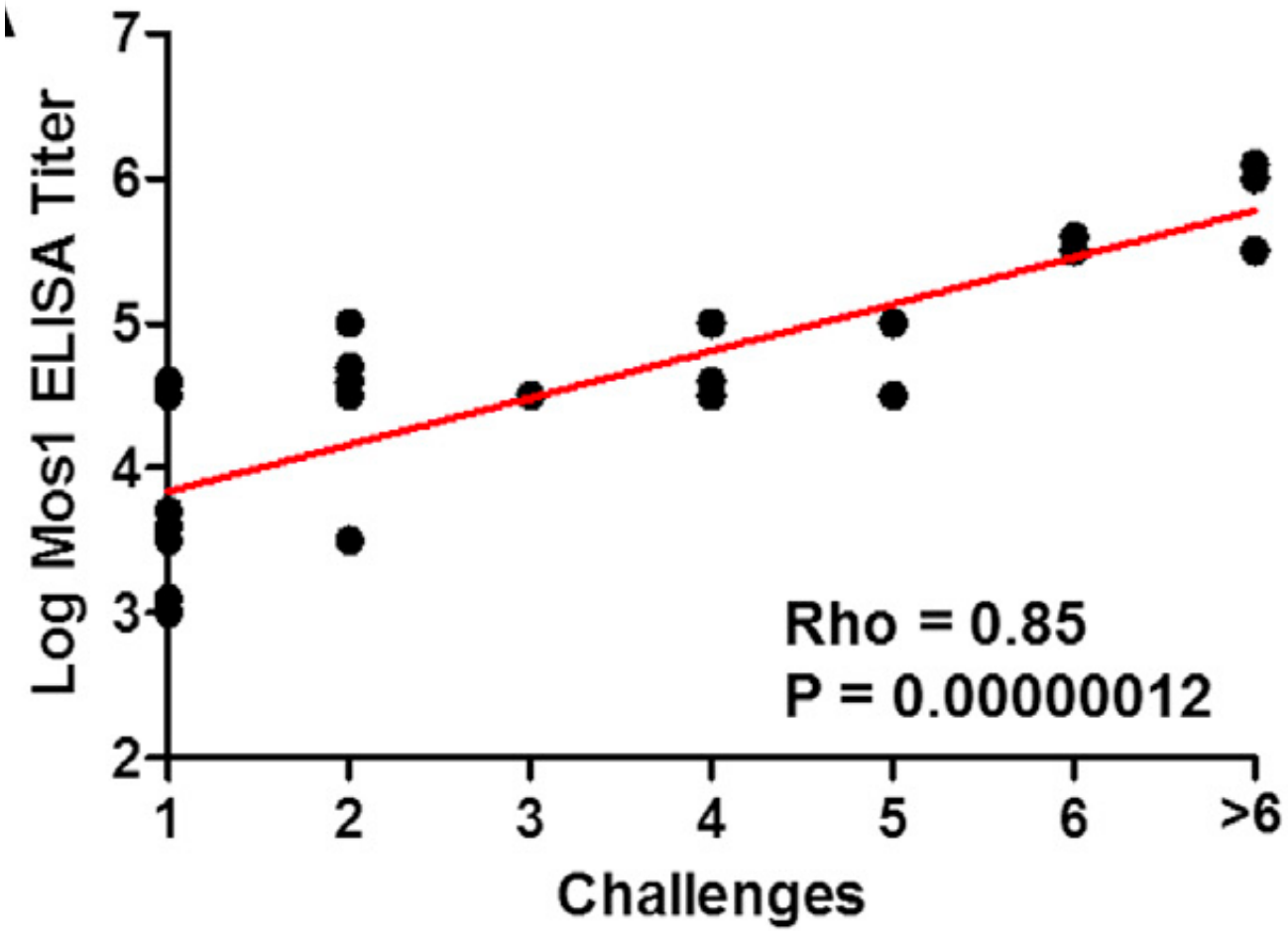
A



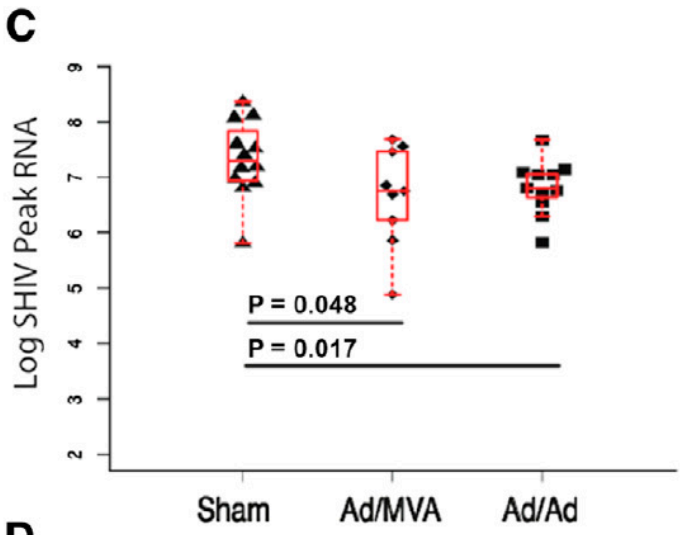
B

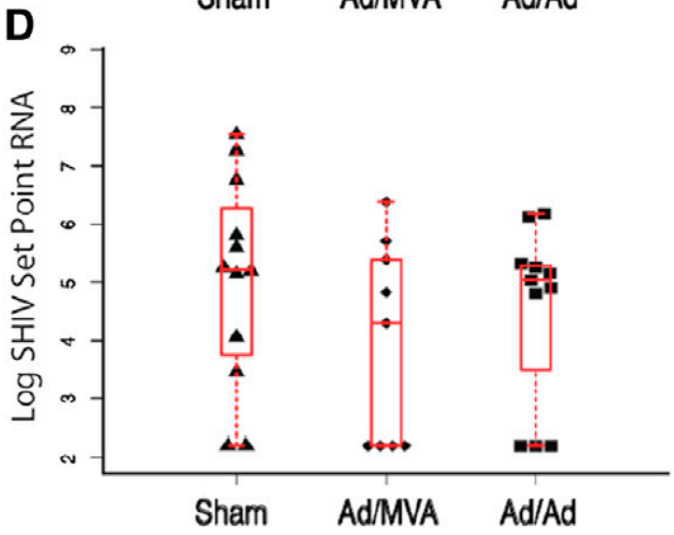
	P-Value vs Sham*	Hazard Ratio (95% Conf. Interval)	Per-Exposure Risk Reduction	% Uninfected Challenge #1	% Uninfected Challenge #3	% Uninfected Challenge #6
Ad/MVA	0.002	0.095 (0.021-0.432)	90%	73%	45%	18%
Ad/Ad	0.007	0.132 (0.030-0.582)	87%	67%	42%	8%
Sham	N/A	1	N/A	17%	0%	0%
	*Cox proportional hazard model					

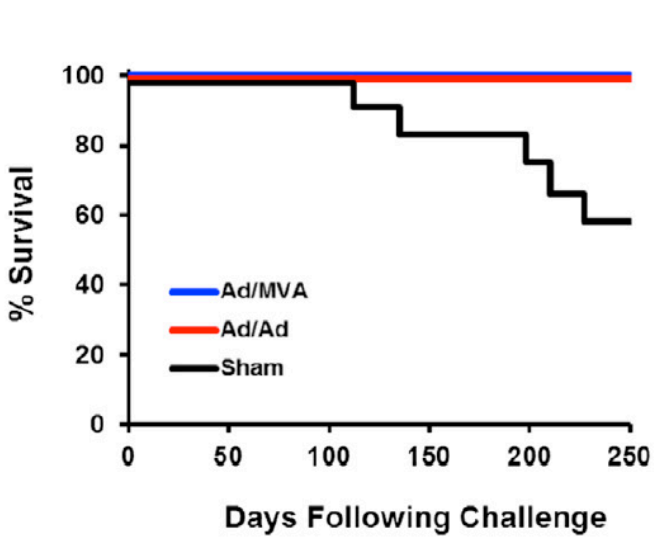
Protection from infection correlates with antibody responses to the vaccine



Mosaic vaccine lowers viremia and enables the macaques to survive SHIV infection







F

	Survival	P-Value vs Sham*
Ad/MVA	100%	0.03
Ad/Ad	100%	0.03
Sham	58%	N/A
	*Fisher's exact test	

Progress for Global Structural Mosaics

Bette Korber

B cell mosaics

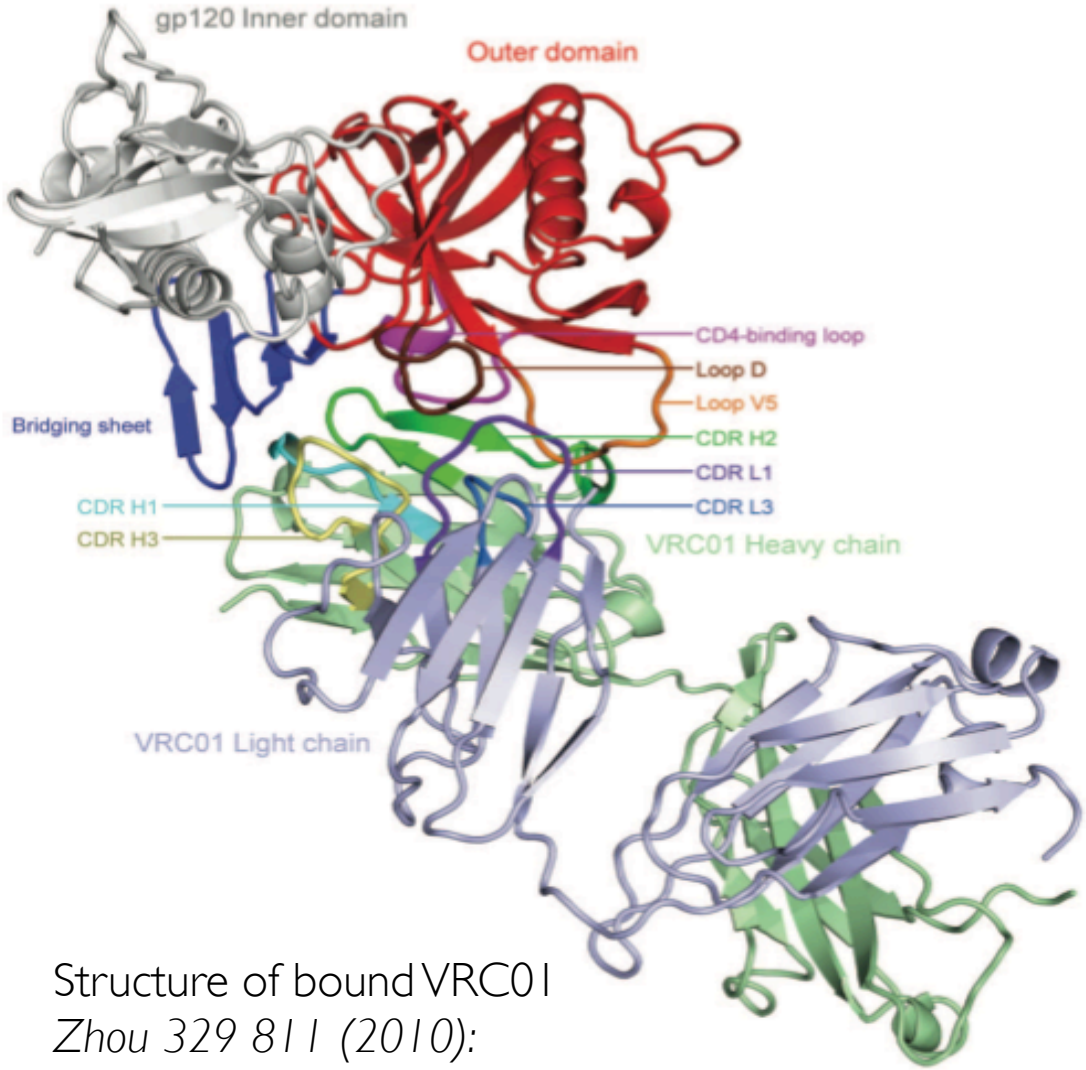
Antibodies recognize regions in folded proteins

1) Input, an Env trimer model:
   Joe Sodroski

2) Determine amino acids in "spheres" surrounding each amino acid in the structure
   Gnana Gnanakaran

2) Define the frequency of each form of each sphere
   Bette Korber

2) Weave a set of 3 proteins that in combination maximize the coverage of the 3 most common forms of each sphere, forbidding the introduction of local combinations of amino acids that are not found in nature.
   Bette Korber/Simon Perkins



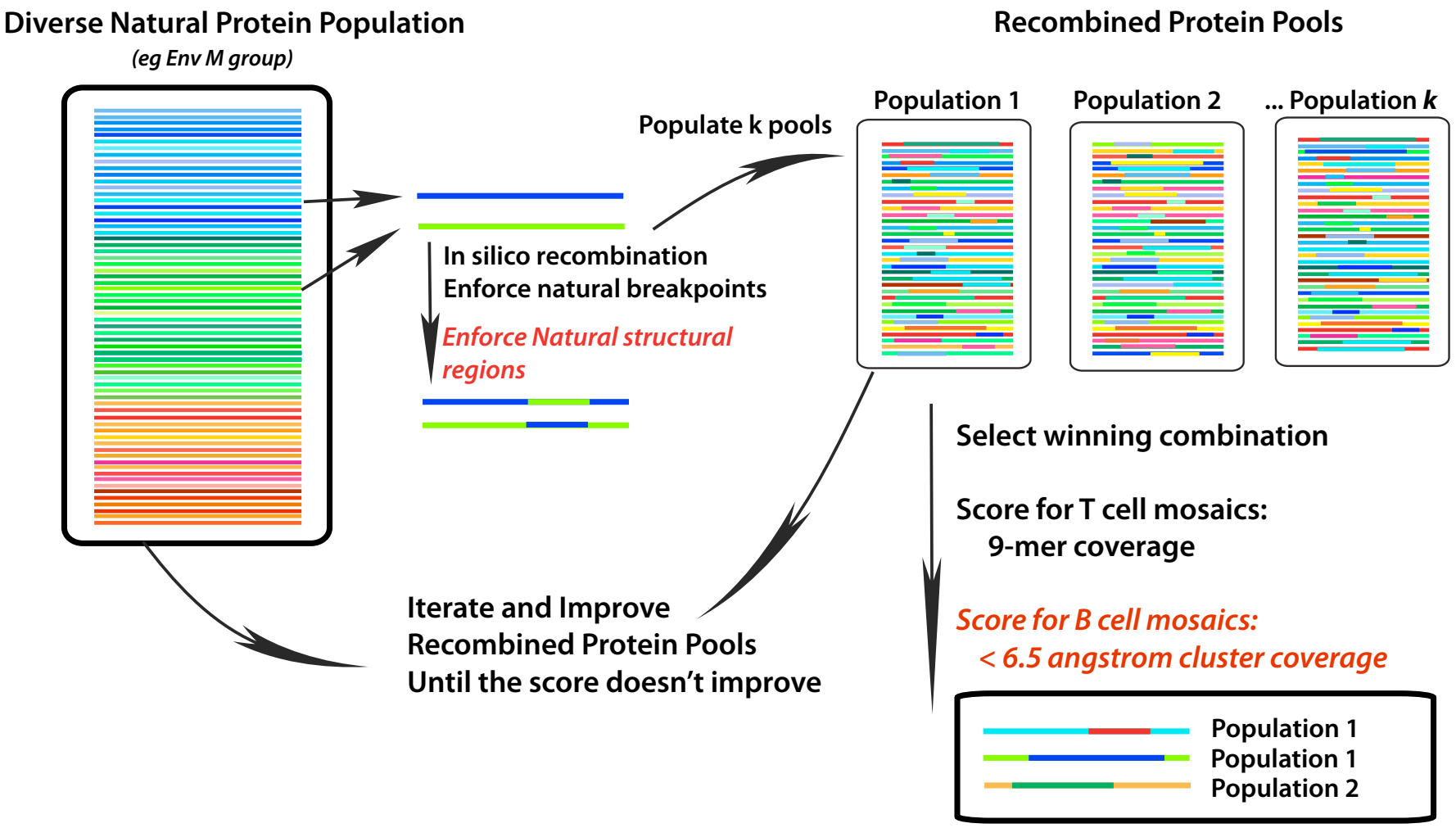
Structure of bound VRC01
Zhou 329 811 (2010):

B cell mosaic: approach

Input:

Protein sequence alignment

Potential B cell Epitope (PBE) position sets (<6.5 angstrom, ≤10 aa clusters)



What's next?

- Two Phase I T cell mosaic trials: safety and immune response
  - Delayed due to a safety issue with the vector, to start in the summer
- Macaque study of structural B cell mosaics:
  - Proteins are functional, bind to "good" antibodies
  - They raise anti-HIV antibodies, we don't know yet if they are neutralizing
- Tailored therapeutic T cell vaccine: design phase
  - Manufacture 6 vaccines, give 2 to an infected person that maximize epitope matches, minimize mismatches
- Epigraphs: design phase
  - Dynamical programming graph theory solution to the T cell mosaic problem. Very fast, optimal solution
  - Mosaics were very nearly optimal, we don't need to remake
- Swarm Vaccines:
  - Vaccinate with viral variants from an individual that made a good neutralizing antibody response
- Signature-based vaccine
  - 2 of 3 functional, being tested at Harvard as immunogens in macaques

Acknowledgements

- T cell mosaics
  - LANL: Simon Perkins (now at Google), Will Fischer
  - Duke: Bart Haynes
  - Harvard: Dan Barouch
- Structural Mosaics
  - Harvard: Joe Sodroski and Jack Mao
  - LANL: Gnana Gnanakaran, Simon Perkins (now at Google)
- Epigraph and Tailored
  - Louis Picker, Klaus Fruh: CMV vector
  - LANL: James Theiler, LANL
- Swarm vaccines
  - Duke: Bart Haynes, Feng Gao, Larry Liao Duke
  - LANL Peter Hraber, Alan Lapedes, Elena Giorgi Tanmoy Bhattacharya
- Signature based vaccines
  - Duke: David Montefiori
  - Harvard: Dan Barouch, Bing Chen
  - LANL: Karina Yusim

Los Alamos NATIONAL LABORATORY

Bill and Melinda Gates Foundation

National Institute of Allergy and Infectious Diseases

CHAVI-ID
Duke Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery

CAVD the collaboration for AIDS Vaccine Discovery